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GALLBLADDER DISEASES IN DOGS AND CATS

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ANATOMY AND PHYSIOLOGY

The biliary system consists of the gallbladder (GB), cystic duct, common bile duct (CBD), hepatic ducts, interlobular ducts, intralobular ducts, bile ductules, and hepatic canaliculi. The GB is a teardrop-shaped organ located in the cranioventral abdomen, attached to the liver to the right of midline within a fossa between the right medial and quadrate liver lobes. The GB acts as a reservoir where bile is stored, modified, and eventually expelled. First, bile is formed in the hepatocytes and is actively secreted into the bile canaliculi. From there, bile flows through the intrahepatic bile duct system (bile ductules - intralobular ducts - interlobular ducts) leaving the liver in the hepatic ducts that finally merge into the CBD after branching off the cystic duct that travels toward the GB. The cystic duct is an important landmark in that it distinguishes the otherwise continuous hepatic ducts from the CBD. At the junction with the intestines, the communication of the CBD and duodenum is anatomically distinct in the dog and cat. After contraction of the GB, bile is released into the CBD and enters the duodenum through the sphincter of Oddi. In the dog, the CBD joins the minor pancreatic duct at the major duodenal papilla. In the cat, the CBD fuses with the major pancreatic duct just before entering the duodenal papilla a few cm caudal to the pylorus. The GB wall of dogs and cats is typically thin-walled (up to 1.5 mm) and the GB volume is approximately 1 mL / kg BW. Its contractions are primarily initiated by cholecystokinin, a peptide hormone secreted in the duodenum in response to fats and proteins entering the small intestine. Bile is primarily composed of cholesterol, lecithin, phospholipids, and bile salts. Bile emulsifies fat and neutralizes acid in partially digested food. The synthesis and secretion of bile acids provides an important method for the excretion of cholesterol. In fact the conversion of cholesterol into bile acids represents the main catabolic escape pathway for cholesterol from the body. This illustrates why hypercholesterolemia is typically seen in cholestatic disease processes.

CHOLECYSTITIS

The term cholecystitis denotes inflammatory conditions of the GB and encompasses a variety of acute and chronic diseases with or without bacterial infections. Whereas cholecystitis in people is usually seen in the context of cystic duct obstruction, the etiology of cholecystitis has not been well characterized in dogs and cats.
Most cases of cholecystitis are associated with conditions leading to prolonged bile stasis with subsequent accumulation of cytotoxic bile acids. The GB epithelium, although normally a robust tissue, is continuously exposed to one of the most noxious agents in the body: a concentrated solution of bile acids detergents. In health, the GB empties the concentrated bile several times a day and is replenished with dilute and less noxious hepatic bile. With prolonged stasis concentrated bile stagnates in the GB lumen. In addition the GB epithelium has relatively high metabolic energy requirements, as it continuously reabsorbs electrolytes and water from the bile. Therefore, in a debilitated, anorectic patient chemical injury to the GB wall may occur. This is why GB mucoceles and cholelithiasis/choledocholithiasis, and rarely biliary neoplasia are known predisposing factors in dogs and cats. Ascending bacterial infection is possible and more commonly found in cases of an advanced extrahepatic biliary stasis.
An important and often overlooked factor is GB wall ischemia. Having only a single source of perfusion (i.e. left branch of the hepatic artery) makes the GB also uniquely susceptible to ischemic necrosis following states of splanchnic vasoconstriction (hypovolemic or distributive shock) or blunt abdominal trauma. Studies in humans showed that capillaries barely filled in acalculous cholecystitis, suggesting that altered microcirculation plays an important role in its pathogenesis. A ruptured necrotic GB should be suspected in dogs with a history of (hypovolemic) shock and abdominal effusion with elevated (above serum) bilirubin concentrations.
Emphysematous cholecystitis is a rare variant of cholecystitis in dogs and cats and may be seen as a biliary complication in diabetic patients. Prolonged hyperglycemia, lowered resistance to ascending bacterial infections due to hypomotility of the sphincter of Oddi, and delayed GB emptying may contribute to the increased risk of emphysematous cholecystitis in diabetic patients.
In addition, infarction and hematogenous spread of bacteria may be involved in septic patients or patients with a distant primary infectious focus. Another well-recognized risk factor for development of acute cholecystitis in humans is the use of total parenteral nutrition (TPN) in critically-ill patients due to complete disuse of gastrointestinal tract and resulting bile stasis. Because cholecystitis is very difficult to diagnose in our patients with multisystemic disease, the relevance of this complication while using TPN has yet to be determined in veterinary medicine.

CLINICAL SIGNS

Cholecystitis may be either acute or chronic in nature. Mild cases are very likely often asymptomatic. Clinical signs can be vague and unspecific and solely consist of intermittent inappetence and occasional vomiting, which is why the diagnosis usually requires a high index of clinical suspicion. More severe cases of acute cholecystitis present with anorexia, weakness, vomiting, abdominal pain and fever. The presence of icterus is variable. Patients that present with acute cholecystitis as a consequence of splanchnic hypoperfusion may solely exhibit classical shock signs, such as tachycardia, tachypnea, prolonged capillary refill time, and weak pulses. Chronic cholecystitis is much more difficult to diagnose. Clinical signs may include intermittent anorexia, vomiting, and postprandial discomfort (i.e. lip smacking, tachypnea, tense abdomen). Pain is likely present but is not always readily detected on examination.

DIAGNOSIS

Laboratory findings vary widely with cholecystitis. A left shift with or without leukocytosis is usually seen and blood smear evaluation shows toxic changes in the neutrophils. Most clinicopathologic changes are consistent with cholestasis or posthepatic biliary disease. It should be noted that serum bilirubin concentrations can even be normal or only minimally increased in the very acute setting.

Radiographic findings vary and will be normal in the majority of patients. Focally diminished serosal detail, consistent with an abdominal effusion, radiodense choleliths or emphysema of the GB or biliary tree are useful information quickly picked up on survey radiographs. Ultrasonography is the current imaging method of choice in veterinary medicine and the GB is usually easy to localize in the right cranial abdomen. The presence of the Murphy's sign (defined as maximum tenderness over the ultrasonographically localized GB) is regarded a reliable indicator of GB inflammation in people. However this is difficult to evaluate in deep-chested dogs with GBs deep below the liver and small dogs and cats, due to close proximity of adjacent organs.

Ultrasonographic findings indicative of GB disease are a thickened GB wall in the absence of hypoalbuminemia. When assessing GB thickness ultrasonographically it should be noted that its thickness depends on the degree of the GB distension (analog to the urinary bladder) and pseudothickening can occur in the postprandial state. Pseudo-thickening of the GB wall may also occur with abdominal effusion as a result of the acoustic interface between fluid and the GB wall. GB wall thickness in biliary disease has not been critically assessed in dogs and cats, but measurements > 2 mm are definitely regarded abnormal and should raise the suspicion of cholecystitis. A double-rim pattern may reflect edema associated with inflammation of the GB, passive congestion, or again severe hypoproteinemia. A discontinuous or striated thickening (alternating hypoechoic and hyperechoic layers) of the GB wall is suspicious for wall necrosis. Diffuse hyperechogenicity of the GB wall may be a sign for mineralization secondary to chronic cholecystitis. Biliary sludge is most likely an incidental finding in dogs, whereas it may indicate biliary disease in cats.[1] The extrahepatic biliary ducts should be assessed down to the papilla for wall thickness, diameter, sludge or stones. It should be noted that GB dilation is not consistently seen in inflammatory cholestatic disease and no ultrasonographic feature allows differentiation between neoplastic or inflammatory disease. Effusions can be either pericholecystic or generalized and can be seen with and without GB rupture. Aspirates of effusion with cholecystitis do not always yield a yellow-brownish bile-like fluid. The ascitic fluid can also be simply turbid in color. Pericholecystic fluid accumulation is usually indicative of advanced disease and should be aspirated and submitted for cytologic examination and bacterial culture. Comparison of total bilirubin concentration in effusion to serum will help confirm bile leakage. Analysis of bilious effusion is usually characterized by increased total nucleated cell counts (> 8.000 cells/mcl) and a preponderance of neutrophils and macrophages. This is also seen in the absence of infection because the chemical properties of bile are extremely irritating for peritoneal surfaces.

Ultrasound-guided percutaneous cholecystocentesis in the absence of signs of emphysematous or necrotic GB disease is the method of choice to obtain GB bile samples for cytologic and bacteriologic examination (aerobic and anaerobic culture). The author prefers a transhepatic approach (because the liver allows for internal compression of the drainage site) using a 22-gauge spinal needle and the patient under sedation. The GB should ideally be emptied completely thus avoiding spillage into the abdominal cavity, this is especially important in cases of concurrent extrahepatic obstruction, as leakage of even small amounts of bile can lead to focal chemical peritonitis, Enterobacteriaceae (E.coli) and Enterococcus are most often isolated, but Streptococcus spp., Enterobacter sp. and Clostridia spp. can also be found found. Although bile is generally believed to be sterile in health,[2] a recent study documented low numbers of E.coli and Enterococcus spp. in healthy control dogs.[3]

TREATMENT

Depending on the patients' history, condition and severity of disease both medical and surgical therapy is available for patients with cholecystitis. Elimination of cholestatic factors and systemic infection is imperative. Medical therapy consists of IV fluids, antibiotics, and analgesics. While morphine has been shown to cause sphincter of Oddi spasms in dogs, buprenorphine does not cause spasms of the sphincter of Oddi in humans and is therefore, in addition to NSAIDs, considered the first choice analgesic in the management of biliary pain.[4] The choice of antibiotic is best determined from cytologic morphology and/or bile cultures obtained by cholecystocentesis, abdominocentesis or at surgery. Cholecystocentesis can also be useful as an emergency therapy in order to decompress the biliary system.[5] The procedure has minimal risk for bile peritonitis when the GB is drained completely during one stick. Vasovagal collapse when sticking the GB may very rarely occur in sick cats, although this is highly unlikely with careful manual advancement of the fine needle using only moderate force. A study from 2007 showed that patients with cholecystitis or biliary obstruction had a significantly higher prevalence of positive culture results, compared with patients with hepatic inflammation. Antibiotic treatment should be continued for a minimum of 4 weeks. Prompt surgical intervention is usually required for necrotizing cholecystitis and cholecystectomy is the treatment of choice. Survival rate among dogs with surgically managed gallbladder disease was high (86%) in a recent study.[6] Dogs tend to have a better prognosis compared to cats; this is especially true when biliary diversion (biliary enterostomy) is needed.

GALLBLADDER MUCOCELE (GBM)

A GBM is characterized by an abnormal accumulation of intraluminal inspissated bile and mucus and usually has a distinct ultrasonographic appearance. Macroscopically, the affected GB is usually distended and contains gelatinous to firm material. Until 10 years ago, GBM were rarely reported in dogs, but have since become established as one of the most common causes of extrahepatic biliary disease in this species. Whether or not this was the result of a true increase in disease prevalence or simply the result of increased detection is unclear. The etiology of this disorder is still unclear. It is possible that various underlying pathologies result in the same end point, or that a combination of abnormalities is required for a GBM to arise. Genetic factors appear to play a substantial role, as breed predilection for the problem exist in Shetland Sheepdogs as well as Cocker Spaniels and Miniature Schnauzers. Shetland sheepdogs seem to be at particularly high risk for GBM formation. A recent genetic analysis indicates that an insertion mutation in ABCB4 is associated with GB disease in Shelties and other breeds.[7] This mutation causes an compromised secretion of phosphatidylcholine across the hepatocyte canalicular membrane. Phosphatidylcholine reduces bile salt cytotoxicity and protects the biliary epithelium from damage. This illustrates that the classic cystic mucinous hyperplasia noted histopathologically in GBM might merely reflect the response of the biliary epithelium to a primary bile abnormality, rather than indicate a primary mucosal disorder. GB dysmotilities have also been suggested as an underlying cause for GBM formation, although cause and effect are not clear. Moreover, recent reports have suggested that concurrent endocrinopathies, primarily hyperadrenocorticism (HAC) and hypothyroidism may predispose patients to GBM formation. A case-control study revealed that dogs with HAC were 29 times more likely to have GBM than dogs without HAC.[8] The association between GBM and hypothyroidism was less clear in that study. Experimental studies in beagles examined the effect of sustained exogenous cortisol excess on biliary function. A shift in the bile acids composition of GB bile in favor of unconjugated and more hydrophobic and therefore more caustic bile acids may result in irritation of the GB epithelium, with subsequent mucinous hyperplasia and eventually GBM formation.[9,10]

CLINICAL SIGNS

Dogs with GBM may present with an acute or chronic course of disease. Patients are frequently evaluated for vomiting, anorexia, lethargy, and abdominal pain. Fever can be due to bacterial cholecystitis and sepsis, but also secondary to sterile bile peritonitis. Icterus is usually apparent dogs with acute disease, while more chronic cases can have only mild hyperbilirubinemia or normal values. It should be noted that some dogs with non-obstructive GBM can solely present with unspecific signs such as intermittent anorexia or apparent postprandial discomfort, while signs of an acute abdomen can be seen with extrahepatic bile duct obstruction, concurrent pancreatitis, or bile peritonitis.

DIAGNOSIS

Clinicopathologic abnormalities cannot differentiate between a GBM or other hepatobiliary disease. Alkaline phosphatase, ALT, GGT and bilirubin are often elevated, although patients with “immature” mucoceles or early disease usually have minor changes. Hypercholesterolemia is seen in cases of biliary obstruction. Neutrophilia with or without left shift and toxic changes in neutrophils can be seen with bacterial and sterile cholecystitis and/or bile peritonitis. While abdominal radiographs may be useful to detect biliary choleliths, decreased serosal detail or possibly free intraabdominal gas in case of a ruptured GB, they are not helpful to definitively diagnose GBM and ultrasonography remains the gold standard. GBM can be distinguished ultrasonographically from biliary sludge by its immobility (in contrast, sludge will be gravity dependent) and the classic stellate / kiwi /starfish appearance. Sludge is more uniformly hyperechoic, and lacks the striated appearance seen with a GBM. The GB wall may be normal or diffusely thickened. Ultrasonographic findings of pericholecystic reaction, localized or generalized echogenic peritoneal fluid, or decreased radiographic peritoneal detail should raise the index of suspicion for GB rupture. Cases of GBM with pericholecystic peritonitis without evidence of GB rupture at surgery do also exist. Also small pockets of free fluid should always be aspirated, examined (TNCC, bilirubin, cytology) (see above), and cultured. Given the association between HAC and GBM, both adrenal glands should concurrently be evaluated for shape and size. If HAC is suspected in dogs presenting with a GBM, endocrine testing should ideally be postponed until stabilization of the patient. This is imperative, as false positive test results may very likely occur in stressed and sick dogs. The incidence of infection is unclear in canine GBM with reported rates ranging from 9.1–66.0%.[11-13] Common isolates include Escherichia coli, Enterobacter, Enterococcus and Clostridium spp. Experimental work suggests that biliary infection stimulates mucin hypersecretion. Bacterial enzymes also may play an inflammatory role by deconjugating bile acids, making them more toxic to GB epithelium. This is why bile should always be cultured aerobically and anaerobically and examined cytologically in patients with a GBM. Bile can either be obtained via ultrasound-guided cholecystocentesis or during surgery. Cholecystocentesis should not be performed in cases of obvious GB wall abnormalities.

GBM is a clinical diagnosis supported by the finding of distinct ultrasonographic features and confirmed macroscopically when thick gelatinous mucin adhering to the luminal GB walls is apparent. Histologically mucoceles are characterized by cystic mucinous hyperplasia and varying degrees of neutrophilic, lymphoplasmacytic or mixed-cell cholecystitis. Depending on the degree of pressure originating from the inspissated bile clump, extensive areas of coagulative necrosis are also seen.

TREATMENT

Surgical removal of the diseased GB is indicated in the majority of patients, this is especially the case when bile peritonitis is present. Cholecystectomy is the most common curative procedure. Rarely intraluminal mucocele contents block the patency of the common bile duct, this is why the ducts should always be examined by catheterization after cholecystotomy or duodenotomy and should be expressible by digital manipulation from the cystic duct towards the duodenum. Cholecystoduodenostomy may be indicated depending on the viability of the

bile duct. However this procedure leaves patients with a permanent opening between their biliary system and gut and a high risk for ongoing ascending hepatobiliary infection. Acute pancreatitis is a common postoperative complication and should be anticipated and treated with analgesics and antiemetics. Although biliary rupture would be intuitively assumed to carry a more guarded prognosis, a retrospective study found no associations between outcome of surgical treatment (survival vs nonsurvival) and preoperative findings, biliary rupture, surgical procedure performed, results of histologic examination of the liver, or development of pancreatitis.[11] Similarly, another retrospective study on the outcome on GB rupture in dogs could document a high survival rate which was not significantly related to presurgical bile leakage, positive results of bacterial culture, or mucocele formation.[6] Survival rate for dogs with GB rupture and bile leakage prior to surgery was 94.4%, for dogs with bacterial bile infection 82.0%, and for dogs with GB mucoceles 81.0%, none of which were significantly different from the overall survival rate.[6]

Medical therapy for GBM is reserved for stable non-icteric patients with compliant owners, as it can be associated with complications. Regular examinations are recommended, including ultrasonographic examination of the GB and serum biochemical analyses, and frequent communication with clients is important. Detection of clinical signs of GB rupture warrants immediate surgical intervention. A combination therapy of choleretics (ursodiol 10-15 mg/kg SID given with food) and antibiotics (ideally based on culture and sensitivity pattern) are most frequently attempted. The probability of concurrent bacterial biliary infection rises with the degree of cholestasis (i.e. non-cholestatic disease is less likely to be infected, as bile is bactericidal). If empiric antibiotic selection becomes necessary, the author suggests an antibiotic that is effective against most enteric gram-negative aerobes and anaerobes that have good biliary penetration (cephalosporins, amoxicillin-clavulanic acid). In addition, low-fat diets are likely beneficial. It is the authors experience that medically treated dogs virtually all end up being treated surgically, as almost all clinical signs from that point onwards will be interpreted as somewhat biliary-related by owners. Also owners ultimately feel uncomfortable with a “ticking time bomb”. An exception may be the hypothyroid dog with a GBM, where medical therapy (thyroxin and ursodiol) may be particularly successful.[14] The underlying causes for GBM formation in hypothyroid dogs is thought to be a combination of dyslipemia (i.e. abnormal biliary cholesterol saturation) and delayed GB emptying. Both conditions would be reversed with administration of adequate amounts of thyroxin.

GALLBLADDER MUCOCELE IN CATS

To the authors knowledge feline GBM has only been reported twice in the literature and the diagnosis in both cases was based mainly on histopathology and not on the classic ultrasonographic appearance of stellate or striated patterns described in dogs. In one icteric cat with concurrent hepatic lipidosis the macroscopic description of GB contents was comparable to typical macroscopic findings in dogs. The ultrasonographic appearance of peripheral immobile echogenic bile in the absence of a striated pattern was suggested to represent an early stage of the disease.[15] The author has seen cases of feline GBM with immobile inspissated echogenic bile and positive bile culture (E.coli) associated with cholecystitis and cholangitis/cholangiohepatitis and duodenitis. It is likely that ascending biliary infections from the duodenum cause epithelial mucinous hyperplasia in this species.

GALLBLADDER NEOPLASIA

Primary tumors of the GB are extremely rare in cats and dogs. The two primary tumors of the biliary system are the biliary cystadenoma and adenocarcinoma; both arise most commonly from the intrahepatic bile ducts. In addition dogs (exceedingly rarely cats) rarely present with neuroendocrine tumors (carcinoid) of the GB.[16-18] Interestingly these tumors are discovered because they hemorrhage into the gastrointestinal tract. Hematemesis, melena, anemia and possibly abdominal pain are the presenting signs. Ultrasonography reveales a hyperechoic mass in the GB. Cholecystectomy may be curative if the tumor is localized to the GB wall without evidence of metastatic spread. Clinicians should be aware of this disease when presented with a patient exhibiting upper gastrointestinal bleeding, where no gastrointestinal bleeding site can be identified.

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